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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/728,521	12/05/2003	Atul Varadhachary	HO-P02703US2	8270

26271 7590 12/05/2005

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 12/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/728,521	VARADHACHARY ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7-10,14-20,26-32 and 38-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7-10,14-20,26-32 and 38-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1, 7-10, 14-20, 26-32 and 38-40 are pending.

Applicants' amendment filed September 19, 2005 is acknowledged. Applicant's response has been fully considered. Claims 1, 8-10, 15, 16, 26-28, 31, 32 and 38 have been amended, and claims 45 and 46 have been cancelled. Therefore, claims 1, 7-10, 14-20, 26-32 and 38-40 are examined.

Withdrawn Claim Rejections - 35 USC § 112

2. The previous rejection of claims 28, 30 and 46 under 35 U. S. C. 112, second paragraph as being indefinite, is withdrawn in view of applicant's cancellation of the claim, and applicant's amendment to the claim in the amendment filed September 19, 2005.

Withdrawn Claim Rejections - 35 USC § 103

3. The previous rejection of claims 45-46 under 35 U. S. C. 103(a) as being unpatentable over by Van Bree *et al.* (WO 01/72322, October 4, 2001), is withdrawn in view of applicant's cancellation of the claim in the amendment filed September 19, 2005.

New Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 7-10, 14-20, 26-32 and 38-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating bacteremia, sepsis, enhancing a mucosal immune response in the gastrointestinal in a subject, decreasing mortality

of a subject having bacteremia or sepsis, comprising administering orally to the subject an effective amount of a lactoferrin composition comprising at least 1% to 50% of an N-terminal lactoferrin variant, wherein the variant has a deletion or substitution of 1 to 16 N-terminal amino acid residues of lactoferrin and has the same biological function as the full length of lactoferrin as indicated in paragraphs [0046] and [0063]; or a method of treating bacterial infection using a pharmaceutical composition comprising an N-terminal lactoferrin variant as indicated in the prior art, does not reasonably provide enablement for a method of treating bacteremia, sepsis, enhancing a mucosal immune response in the gastrointestinal in a subject, decreasing mortality of a subject having bacteremia or sepsis, comprising administering orally to the subject an effective amount of a lactoferrin composition comprising at least 1% to 50% of an N-terminal lactoferrin variant, where the structure and function of the N-terminal lactoferrin variant are not defined. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1, 7-10, 14-20, 26-32 and 38-40 are directed to a method of treating bacteremia, sepsis, enhancing a mucosal immune response in the gastrointestinal in a subject, decreasing mortality of a subject having bacteremia or sepsis, comprising administering orally to the subject an effective amount of a lactoferrin composition comprising at least 1% to 50% of an N-terminal lactoferrin variant. The specification, however, only discloses cursory conclusions without data supporting the findings, which states that the instant invention is directed to a method for treating bacteremia, sepsis, septic shock or related conditions, the method comprising oral administration of a lactoferrin composition, which comprises lactoferrin or an N-terminal lactoferrin variant in

which at least the N-terminal glycine residue is truncated or substituted, or lactoferrin lacking one or more N-terminal residues or having one or more substitutions in the N-terminal (page 4, paragraphs [0011] and [0012]). There are no indicia that the present application enables the full scope in view of the method of treating bacteremia, sepsis, septic shock or related conditions using a lactoferrin composition comprising an N-terminal lactoferrin variant as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the absence or presence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding the N-terminal lactoferrin variants in the method of treating bacteremia, sepsis, septic shock or related conditions, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

Examples 3-6 indicate the use and effect of rhLF in the murine LPS model of sepsis and bacteremia; Example 16 indicates using rhLF in the reduction of mortality and key cytokines in sepsis; and Example 17 indicates anti-sepsis effect of three different rhLF preparations containing different percentage of N-1 truncates. However, there are no other working examples indicating the effects of various N-terminal lactoferrin variants in the treatment.

(3). The state of the prior art and relative skill of those in the art:

The prior art (e.g., Van Bree *et al.*, WO 01/72322) teach human lactoferrin (hLF) or LF variants (e.g., N-terminal variants), which have the biological activities of natural LF, can be used to treat large scale (bacterial) infection or blood-borne infection (sepsis); and Nuijens et al. (USPN 6,333,311) teach lactoferrin variants with one or more arginine residues in the N-terminal region deleted are used for treating inflammation. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the identification of functional N-terminal lactoferrin variants and their effects in the treatment to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass a method for treating bacteremia, sepsis or related conditions, comprising administering orally to the subject an effective amount of a lactoferrin composition comprising at least 1% to 50% of an N-terminal lactoferrin variant. Although the specification indicates the use of specific N-terminal lactoferrin variant (e.g., N-1 truncate) in treating sepsis, the specification has not demonstrated the effects of various N-terminal lactoferrin variants in the treatment, the invention is highly unpredictable regarding the structures of functional N-terminal lactoferrin variants and their effects in the treatment.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method for treating bacteremia, sepsis or related conditions, comprising administering orally to the subject an effective amount of a lactoferrin composition comprising at least 1% to 50% of an N-terminal lactoferrin variant. The specification indicates

the use and effect of rhLF in the murine LPS model of sepsis and bacteremia (Examples 3-6), the use of rhLF in the reduction of mortality and key cytokines in sepsis (Example 16), and anti-sepsis effect of three different rhLF preparations containing different percentage of N-1 truncates (Example 17). However, the specification does not demonstrate the effects of various functional N-terminal lactoferrin variants in the treatment. Furthermore, the specification does not provide any specific guidance on the identification of functional variants. Since the specification does not provide sufficient teachings on the identification of functional variants, therefore, it is necessary to carry out undue experimentation to assess the effect of N-terminal variant in treating bacteremia, sepsis or related conditions.

(6). Nature of the Invention

The scope of the claims encompass a method for treating bacteremia, sepsis or related conditions, comprising administering orally to the subject an effective amount of a lactoferrin composition comprising at least 1% to 50% of an N-terminal lactoferrin variant, however, the specification does not demonstrate the effect of N-terminal variant in treating bacteremia, sepsis or related conditions. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed methods associated with variants, the effect of N-terminal lactoferrin variant in the treatment is unpredictable, and the teachings in the specification are limited, therefore, it is necessary to carry out undue experimentation to identify the functional variants and to assess their effects in the treatment.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 8-10, 15 and 16, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claim 8 recites the limitation "said lactoferrin composition comprises mammalian lactoferrin" in line 1. There is insufficient antecedent basis for this limitation in the claim because claim 1 only recites the lactoferrin composition comprises an N-terminal lactoferrin variant, the claim does not indicate the composition comprises lactoferrin. See also claims 9-10, 15 and 16.

Response to Arguments

Applicant indicates claims 8-10, 15 and 16 have been amended, and the specification, (specifically, paragraphs [0042] and [0069]) describes that the lactoferrin composition comprises lactoferrin, a portion or part of lactoferrin, an N-terminal lactoferrin variant or a combination thereof. Thus, one of skill in the art would understand that the composition could comprise lactoferrin, as well as about 1% to about 50% N-terminal variant (pages 5-6 of the response).

Applicant's response has been considered, however, the argument is not found persuasive because the independent claim, claim 1, only recites the lactoferrin composition comprise an N-terminal lactoferrin variant, it does not indicate the composition comprises a combination of lactoferrin and an N-terminal lactoferrin variant. Thus, one of skill in the art would not know the lactoferrin composition would comprise lactoferrin besides an N-terminal lactoferrin variant.

7. Claim 9 is indefinite because of the use of the term "said lactoferrin composition comprises human or bovine". The term cited renders the claim indefinite, it is not clear what material from human or bovine is contained in the lactoferrin composition.

Maintained Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Previous rejection of claims 1, 7-10, 14-19, 26-32 and 38-40 under 35 U.S.C. 103(a) as being unpatentable over by Van Bree *et al.* (WO 01/72322, October 4, 2001) is maintained, and the response to argument is shown below.

Van Bree *et al.* teach human lactoferrin (hLF) can block free LPS and cause them to clear from the body more rapidly, and mask their inflammatory activity; and hLF or LF variants (e.g., N-terminal variants, hLF-2N, hLF-3N, hLF(1-11), hLF(2-11) and hLF(3-11); pages 4, 5 and 27), which have the biological activities of natural LF, can be used to treat large scale (bacterial) infection, blood-borne infection (sepsis) as well as inflammation resulting from an infection (pages 3-4; page 20, lines 24-29; page 24; claims 1, 8, 9), where the concentration of the polypeptide (LF or LF variant) in the pharmaceutical composition can be at least 1% to 20% by weight, or the peptide/fragment can be administered about 0.19 mg/kg to 19 mg/kg daily (corresponding to 10-100 mg/kg of intact lactoferrin; about 11.4 mg to 114 mg daily assuming weight of a person is about 60 kg; page 24; claims 15, 16). The lactoferrin variants can be produced by proteolytic cleavage of LF or recombinant technique (pages 11-13; claim 10); and

lactoferrin/variant can be administered orally in the form of a solid or solution, and the active components can be encapsulated in gelatin capsules together with inactive ingredients and carriers such as glucose, mannitol or magnesium carbonate (an antacid; claim 14), and the formulated solid or liquid formulations can be in an enteric-coated form (page 26; claims 7, 17-19). Although the reference does not provide a specific example for a method of treating bacteremia, enhancing a mucosal immune response or decreasing mortality using a lactoferrin composition containing the N-terminal variant, it indicates a high dose of hLF or LF variant (e.g., N-terminal variant) having the biological activity of natural LF can be orally administered in the treatment, which has the same method step as the claimed invention, thus at the time of invention was made, it would have been obvious to one of ordinary skill in the art to orally administer N-terminal variant of LF in the method of treating bacteremia, enhancing a mucosal immune response or decreasing mortality to produce the desired effect as the LF (claims 26-32, 38-40), which results in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

Response to Arguments

Applicant indicates Van Bree *et al.* describe the concentration of the lactoferrin polypeptide (lactoferrin or lactoferrin variant) can vary widely from about 0.1% to 20% by weight of the pharmaceutical composition. Thus, the total concentration of lactoferrin in the composition is 0.1% to about 20% with the remaining 99% to 80% of the composition being pharmaceutical carriers. The present claims refer to not the total concentration of lactoferrin in the pharmaceutical composition, but the amount of N-terminal lactoferrin variant compared to non N-terminal lactoferrin variant (See paragraph [0077]). In view of this distinction, Applicants

assert that no where in Van Bree et al. is there a suggestion of the total lactoferrin concentration comprising at least 1% to at least 50% is an N-terminal lactoferrin variant (pages 6-7 of the response).

Applicants' response has been considered, however, the argument is not found persuasive because the specification (paragraph [0077]) clearly indicates "the composition of the present invention comprises a lactoferrin concentration of about 0.0001% to about 30%", and the term "lactoferrin composition" is defined as a composition having lactoferrin, a portion or part of lactoferrin, an N-terminal lactofenin variant, or a combination thereof (paragraph [0042]), thus, it appears that any composition, as long as it contains sufficient amount of lactoferrin, a portion or part of lactoferrin, an N-terminal lactofenin variant, or a combination thereof in the composition (e.g., 0.0001%-30% by weight), would meet the criteria of "lactoferrin composition". The specification does not indicate the amount of N-terminal lactoferrin variant has to be compared to non N-terminal lactoferrin variant in the composition. Therefore, the teachings of Van Bree *et al.* that indicate the concentration of the polypeptide (LF or LF variant) in the pharmaceutical composition is at least 1% to 20% by weight (page 24, lines 10-12; page 25, lines 22-24) meet the criteria of "a lactoferrin composition" in the claims.

Conclusion

9. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Patent Examiner

CHIH-MIN KAM
PATENT EXAMINER

CMK
December 1, 2005